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Original Research Article

Effect of Jinlida granule on glycolipid metabolism, oxidative stress, and inflammatory factors in type 2 diabetes mellitus patients with non-alcoholic fatty liver disease

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Abstract

Purpose: *To investigate the effect of Jinlida granule on glycolipid metabolism, oxidative stress, and inflammatory factors in type 2 diabetes mellitus (T2DM) patients with non-alcoholic fatty liver disease (NAFLD).*
Methods: *A total of 132 T2DM patients with NAFLD were equally and randomly divided into study and control groups. Patients in the control group were treated with non-drug therapy including routine diet control, exercise, alcohol avoidance, and drug therapy (using blood glucose and lipid lowering drugs). The study group was treated with Jinlida granule in addition to other measures used in the control group. Blood glucose, blood lipid, and liver function parameters were compared after treatment. Nesfatin-1, oxidative stress, inflammatory factors, liver fat content, and degree of fibrosis were assessed. The efficacy and potential mechanism of Jinlida granule in the patients were assessed.*
Results: *Blood glucose, lipid, and liver function parameters in the study group were lower than in the control group following treatment. Nesfatin-1, GSH-Px, and adiponectin levels were higher, while MDA, TNF-α, liver fat, LSM and CAP levels were lower than in the control group ($p < 0.05$). The response rate of the study group was 96.97 %, which was higher than the 87.88 % in the control group ($p < 0.05$). The incidence of adverse drug reactions in the two groups during treatment was comparable ($p > 0.05$).*
Conclusion: *Jinlida granule exerts positive effect on T2DM patients with NAFLD. Thus, Jinlida granule has potentials for application as an adjuvant in the treatment of T2DM with NAFLD.*

Keywords: *Type 2 diabetes mellitus, Non-alcoholic fatty liver disease (NAFLD), Jinlida granule, Glycolipid metabolism, Oxidative stress, Inflammatory factors*

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INTRODUCTION

Surveys have indicated that the prevalence of diabetes in Chinese adults is 9.7 %, of which Type 2 Diabetes Mellitus (T2DM) accounts for about 90 %. There are an estimated 20 % of T2DM patients with non-alcoholic fatty liver disease (NAFLD) among the T2DM patients [1].

Type 2 Diabetes Mellitus patients with NAFLD are common in clinical practice, and fatty liver increases the risk of glucose metabolism disorders, while T2DM also promotes the occurrence of fatty liver and liver injury. At present, diet and lifestyle interventions are the primary treatment for NAFLD, and there is no effective drug therapy. Traditional Chinese medicine (TCM) attributes T2DM and NAFLD to the categories of “fatty liver”, turbid phlegm” and “stagnation of blood”. The TCM has a certain effect on the treatment of T2DM with NAFLD [2].

Jinlida granule is a Chinese herbal preparation developed according to the theory of spleen treatment. It functions in fortifying the spleen and boosting Qi, removing blood stasis and eliminating dampness, as well as increasing blood flow to the liver and rectifying Qi. It also plays a role in controlling blood glucose in T2DM and treating T2DM-related metabolic fatty liver and peripheral neuropathy in T2DM [3]. This study analyzes the efficacy of Jinlida granules in treating T2DM with NAFLD, and the effect of Jinlida granules on the levels of oxidative stress and inflammatory factors in affected patients. The study attempts to investigate the clinical value and potential mechanism of Jinlida granule in the treatment of T2DM with NAFLD, providing a reference for the clinical practice of the Jinlida granule.

METHODS

Patients

A total of 132 T2DM patients with NAFLD admitted to the People’s Hospital of Shijiazhuang, Shijiazhuang City, from June 2020 to June 2021 were included in the study. The diagnostic criteria include: T2DM was diagnosed according to the relevant criteria established by the World Health Organization in 1999 [4]; NAFLD was diagnosed according to the Guidelines for the Diagnosis of Nonalcoholic Fatty Liver Disease, formulated by the Chinese Society of Hepatology [5].

Inclusion criteria

Patients who met both diagnostic criteria related to T2DM and NAFLD; and patients who were informed and able to cooperate to complete this study were included.

Exclusion criteria

Patients with type 1 diabetes; pregnant or lactating women; patients who use drugs affecting glucose and lipid metabolism within 3 months prior to participating in the study; patients with concurrent infection; patients with acute complications related to T2DM; patients with severe dysfunction of vital organs; patients with cardiovascular disease, autoimmune diseases; and patients with liver disease caused by other reasons were excluded from the study. A total of 132 T2DM patients with NAFLD were divided into study group and control group via utilizing random number table, with 66 patients in each group. The study group consisted of 36 males and 30 females aged 35 - 60 years with mean age of 47.45 ± 10.48 years. Body mass index (BMI) was 23 - 32 kg/m^2, and mean BMI was 27.45 ± 3.15 kg/m^2. The control group consisted of 35 males and 31 females aged 34 - 61 years, and the mean age was 48.09 ± 10.37 years, BMI was 23 - 32 kg/m^2, and mean BMI was 28.04 ± 3.34 kg/m^2. The general data between the two groups were compared, and the differences indicated no statistical significance ($p > 0.05$).

Ethical matters

All procedures involving human participants were approved by the Ethics Committee of The People’s Hospital of Shijiazhuang (approval no. 20180710), and carried out in accordance with the guidelines of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [6]. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Treatments

Both groups were treated with non-drug therapy such as routine diet control, exercise, alcohol avoidance, along with 500 mg metformin (Disha Pharmaceutical Group Co. Ltd, National Medicine Permission no. H20103615) three times a day, and 10 mg atorvastatin (Changzhou Yabang Pharmaceutical Co., Ltd., national medicine permission no. H20153280) once a day. In addition to this, the study group took 9 mg Jinlida granule (Shijiazhuang Yiling Pharmaceutical Co. Ltd, National Medicine permission no. Z20050845) three times a day. Medication intervention was continued for 3 months.

Parameters evaluated

Blood glucose, blood lipid and liver function enzymes levels

Blood glucose, blood lipid and liver function enzymes levels were compared between the groups before and after treatment by collecting 5

mL peripheral venous blood. Fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using EXC800 automatic biochemical analyzer (Zhongyuan Huiji Biotechnology Co. Ltd). The LD-600 automatic glycosylated hemoglobin analyzer (Labnovation Technologies, Inc.) was employed to determine glycosylated hemoglobin A1c (HbA1c), DH-100T automatic electrochemiluminescence immunoassay analyzer (Hunan Dymind Biotechnology Co. Ltd) was used to determine fasting insulin (FINS), and insulin resistance index (HOMA-IR) was calculated using Eq 1.

HOMA-IR = {(FPG × FINS)/22.5} …… (1)

Nesfatin-1, oxidative stress indicators and inflammatory factor levels

Nesfatin-1, oxidative stress indicators (malondialdehyde (MDA) and glutathione peroxidase (GSH-Px)), inflammatory factor indicators (tumor necrosis factor-α (TNF-α), and adiponectin levels) were measured by enzyme-linked immunosorbent assay (ELISA). Nesfatin-1 ELISA kit was purchased from RayBiotech (Germany), and MDA and GSH-Px ELISA kit were purchased from Nanjing Jiancheng Bioengineering Institute. The TNF-α and adiponectin ELISA kits were purchased from Invitrogen (USA).

Controlled attenuation parameter and liver stiffness measurement

Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) of liver fat were recorded using an ultrasound transient elastography. Liver fat content = 62.592 × standardized ultrasound hepatic / renal ratio - 27.863.

Treatment effectiveness/efficacy

According to relevant standards of the Guiding principles for clinical research on new drugs of Traditional Chinese medicine, the outcomes are represented as marked response, moderate response and no response. Marked response refers to disappearance of clinical symptoms, normal blood glucose and blood lipid levels. Elimination of fatty liver in imaging examination, and restoration of normal liver function after treatment. Moderate response referred to significantly improved clinical symptoms of patients, decreased blood glucose and blood lipid levels, and decreased fatty liver by more than 1 grade in imaging examination. No response referred to no improvement in blood glucose, blood lipid levels and liver function of patients after treatment.

Adverse reactions

A compilation of the incidence of drug-related adverse reactions during treatment in the two groups was compared.

Statistical analysis

Data were processed using Statistical Package for the Social Sciences (SPSS) 19.0 software. Measurement data were expressed as mean ± standard deviation (SD), and independent sample *t*-test was adopted to compare the means between the two groups. Paired *t*-test was used to compare the means before and after treatment, and enumeration data were expressed as case number. Chi-squared (χ^2) test was employed to compare the two groups, and rank sum test was adopted for ranked data. $P < 0.05$ indicated statistical significance.

RESULTS

Blood glucose, lipid levels and liver function

After treatment, the levels of blood glucose parameters (FPG, FINS and HOMA-IR), blood lipid indices (TG and TC) and liver function indices (ALT and AST) in the two groups decreased significantly when compared with that before treatment ($p < 0.05$; Table 1). Furthermore, the levels in the study group were significantly lower than the control group when both were compared after treatment ($p < 0.05$).

Serum Nesfatin-1, oxidative stress and inflammatory factor levels

After treatment, the serum Nesfatin-1, GSH-Px, adiponectin levels increased, while the levels of oxidative stress, index MDA, and inflammatory factor TNF-α levels decreased in comparison with those before the treatment in both groups ($p < 0.05$; Table 2). Furthermore, the Nesfatin-1, GSH-Px and adiponectin levels in the study group were higher than those in the control group, while the MDA and TNF-α levels were lower than those in the control group, ($p < 0.05$).

Liver fat content and fibrosis levels

After the treatment, the liver fat content, LSM and CAP levels in the two groups reduced, and were lower than those in the same group before the

treatment ($p < 0.05$) (Table 3). Besides, after the treatment, the liver fat, LSM and CAP levels in the study group were lower than those in the control group ($p < 0.05$).

Treatment effectiveness/efficacy

The response rate in the study group was higher than that in the control group ($p < 0.05$; Table 4).

Incidence of adverse drug reactions

The rate of adverse drug reaction was compared between both groups during the treatment ($p > 0.05$; Table 5).

DISCUSSION

As a disease that excludes causes like alcoholism, drugs, and viruses, the NAFLD is characterized with excessive lipid droplet deposition in hepatocytes. The pathogenic mechanism of NAFLD remains obscure. However, NAFLD is associated with insulin resistance and is involved in T2DM pathogenesis, while T2DM aggravates liver injury in NAFLD patients. The NAFLD still lacks specific treatment modalities, and non-drug treatments such as diet control, lifestyle changes, and fat reduction are still the main treatment.

Due to the influence of individual self-control and living environment, non-drug treatment is often poor in its efficacy, and at the same time, the presence of NAFLD will increase the difficulty in blood glucose control in T2DM patients and adversely affect the prognosis of patients [7]. It is essential to probe the treatment regimens for T2DM with NAFLD that will be effective in improving the prognosis of the disease.

The popularization of traditional Chinese medicine in clinical practice has resulted in achieving good efficacy in diverse disease [8]. It is believed in TCM that congenital deficiency of the liver, spleen, and kidney is the core element inducing this disease, followed by acquired factors like improper diet, over eating fats and sweets, excessive fatigue, and emotional disorders. Congenital deficiency is coupled with eating and emotional disorders, damp-phlegm in the body, dys-splenism, heat and blood stasis, giving rise to Qi and phlegm stagnation, which are coagulated under the ribs. This is the main pathogenesis of T2DM with NAFLD [9]. Therefore, the treatment of T2DM with NAFLD is based on dispelling evil and supporting right, removing dampness and stasis, rectifying Qi, and transforming phlegm, along with strengthening spleen and kidney.

Jinlida granule is a Chinese herbal preparation developed by TCM based on the theory of spleen treatment, the principle of nourishing spleen and body fluid, and smoothening spleen collaterals. Ginseng serves as the monarch drug to rectify Qi, and fortify the spleen. Rhizoma Polygonati, Rhizoma Atractylodis, and Radix Sophorae Flavescentis serve as the main constituents to clear heat and moisten dryness, as well as tonify the spleen and kidney. Ophiopogon japonicus, Radix Rehmanniae, Fructus Corni, Polygonum multiflorum Thunb., Poria cocos, Rhizoma Coptidis Macrocephalae, Rhizoma Anemarrhenae, Radix Salviae Miltiorrhizae, Herba Epimedii and Herba Eupatorii are adjuvant drugs to replenish essence and Qi, enrich yin and supplement the blood, and enliven the spleen and resolve dampness. Kudzuvine root and litchi serve as envoy drugs to disperse stasis and promote Qi, engender liquid, and allay thirst. Each herb performs its duties and exerts the effects of invigorating the spleen and Qi, removing blood stasis and phlegm, and smoothing the liver, and rectifying Qi [10].

In this study, it was observed that the use of Jinlida granule is based on conventional non-drug intervention and treatment of lowering blood glucose and blood lipid and protecting liver. This can further improve the blood glucose and lipid and liver function levels in T2DM patients with NAFLD, and reduce the liver fat content and the degree of liver fibrosis, thereby improving therapeutic effect.

However, the specific mechanism of Jinlida granule in the treatment of T2DM with NAFLD is still in the research stage. This study has showed that after the treatment intervention, there was a significant rise in the serum levels of Nesfatin-1, GSH-Px and adiponectin, and a significant decrease in MDA and TNF-α in patients who took Jinlida granule in the study group after the treatment. Nesfatin-1 is involved in maintaining glucose homeostasis, food intake and energy metabolism.

It is decompensated in T2DM patients, and its analysis is significant in T2DM development [11]. Both GSH-Px and MDA are oxidative stress-related indices, and TNF-α and adiponectin are inflammatory factors [12]. The results indicated that Jinlida granules could effectively improve inflammatory and oxidative stress response, increase serum Nesfatin-1 level, and regulate blood glucose and blood lipid metabolism in T2DM patients with NAFLD.

Table 1: Comparison of blood glucose, blood lipid and liver function indices before and after treatment (mean ± SD, n = 66)

Group		FPG (mmol/L)	FINS (mU/L)	HOMA-IR	TG (mmo/L)	TC (mmo/L)	ALT（IU/L）	AST (IU/L)
Study	Before treatment	9.31±1.82	9.66±1.65	4.11±0.85	2.89±0.45	5.56±1.05	40.56±8.69	32.41±6.69
	After treatment	6.68±1.76[a]	6.81±1.28[a]	2.03±0.45[a]	1.78±0.57[a]	4.22±1.14[a]	22.74±6.25[a]	17.85±3.57[a]
Control	Before treatment	9.28±1.84	9.69±1.74	4.13±0.79	2.91±0.42	5.61±1.25	41.02±7.69	33.07±7.03
	After treatment	7.33±1.69[a]	8.32±1.41[a]	2.82±0.42[a]	2.27±0.51[a]	4.63±1.17[a]	29.42±5.77[a]	24.12±4.19[a]
Comparison between the two groups after treatment	*t*	2.164	6.442	10.426	5.205	2.039	6.380	9.254
	P-value	0.032	< 0.001	< 0.001	< 0.001	0.044	< 0.001	< 0.001

[a]*P* < 0.05 when compared to the value before treatment within group

Table 2: Comparison of serum Nesfatin-1, oxidative stress and inflammatory factor levels before and after treatment (mean ± SD, n = 66)

Group		Nesfatin-1 (ng/mL)	MDA (μmol/L)	GSH-Px (U)	TNF-α (ng/L)	Adiponectin (mg/L)
Study	Before treatment	0.86±0.21	7.61±1.37	123.25±16.58	19.15±3.69	3.66±0.56
	After treatment	1.19±0.28[a]	4.08±1.27[a]	186.69±20.25[a]	11.08±2.47[a]	6.53±0.79[a]
Control	Before treatment	0.84±0.23	7.72±1.45	125.04±19.87	19.39±3.85	3.61±0.63
	After treatment	0.96±0.24[a]	5.83±1.36[a]	156.69±23.15[a]	14.68±3.02[a]	5.65±1.01[a]
Comparison between the two groups after treatment	*t*	5.067	7.640	7.924	7.496	5.575
	P-value	<0.001	<0.001	<0.001	<0.001	<0.001

[a]*P* < 0.05 when compared to the value before treatment within group

Table 3: Comparison of liver fat content and fibrosis levels before and after the treatment (mean ± SD, n = 66)

Group		Liver fat	LSM (kPa)	CAP (dB/m)
Study	Before treatment	59.58±8.96	14.07±2.58	281.15±31.15
	After treatment	51.11±9.04[a]	8.07±2.11[a]	221.07±33.87[a]
Control	Before treatment	60.24±8.45	13.94±3.04	283.41±35.27
	After treatment	54.58±8.17[a]	9.97±2.09[a]	245.13±32.79[a]
Comparison between the two groups after treatment	*t*	2.324	5.197	4.146
	P-value	0.022	<0.001	<0.001

[a]*P* < 0.05 when compared to the value before treatment within group

Table 4: Comparison of treatment effect between the two groups (n=66; %)

Group	Significantly effective	Effective	Ineffective	Response rate
Study	34 (51.52)	30 (45.45)	2 (3.03)	64 (96.97)
Control	25 (37.88)	33 (50.00)	8 (12.12)	58 (87.88)
χ^2	-	-	-	3.895
P-value	-	-	-	0.048

Table 5: Comparison of incidence of adverse drug reactions between the two groups during the treatment (n = 66; %)

Group	Dizziness	Nausea and vomiting	Total
Study	1 (1.52)	0 (0.00)	1 (1.52)
Control	1 (1.52)	1 (1.52)	2 (3.03)
χ^2	-	-	0.000
P-value	-	-	1.000*

**P* > 0.05 not significantly different

As shown in modern pharmacological studies, ginsenoside, ginseng polysaccharide, polygonatum polysaccharide, atractylodin, and terpenes from Cornus Fructus extracted from Jinlida granules have multiple effects such as lowering blood glucose, repairing islet B cells and regulating lipid metabolism. Besides, they also function in counteracting oxidative stress, anti-inflammation and improving autoimmunity [13]. These effects can lead to changes in serum Nesfatin-1, oxidative stress and inflammatory factors levels in T2DM patients with NAFLD after the use of Jinlida granules, suggesting that Jinlida granules may exert therapeutic efficacy by promoting blood glucose regulation and reducing oxidative stress and inflammatory response in the body. However, the specific mechanism still needs to be further investigated.

Limitations of this study

This study was a single-center study, and the sample size of the included cases was not large enough. Thus, the resulting findings may be biased. Subject to the research design and experimental conditions, the current study does not explore the specific mechanism of Jinlida granule in treating T2DM with NAFLD.

CONCLUSION

Jinlida granules exert anti-oxidative and anti-inflammatory effects, and its use improves the levels of blood glucose and lipid, and also reduce the degrees of liver fat and fibrosis in T2DM patients with NAFLD. Thus, these findings provide novel ideas and strategies for the treatment of T2DM with NAFLD with minimal adverse effect. It has a prospect as an adjuvant in the treatment of T2DM with NAFLD.

DECLARATIONS

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None provided.

Ethical approval

The approval for this study was granted by the Ethics Committee of The People's Hospital of Shijiazhuang (approval no. 20180710),

Availability of data and materials

The datasets used and/or analyzed during the

current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jing Cai and Xue Xia designed the study and carried them out, Jing Cai, Xue Xia, Jingmin Qiao, Ying Gao, Hongyan Li and Yiran Liu supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript.

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